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URINARY METABOLITES OF HYDRAZINE IN MALE FISCHER 344 RATS FOLLOWING INHALATION OR INTRAVENOUS EXPOSURE

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

BRUCE O. STUART, PhD
Director Toxic Hazards Division
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The feasibility of developing an analytical method with urine to determine the extent of a worker's exposure to hydrazine was studied. Urinary levels of hydrazine and two metabolites, monoacetylhydrazine and diacetylhydrazine, were identified and quantified from hydrazine-exposed male rats. The levels of hydrazine recovered from intravenous or inhalation exposures were compared. For all exposures, the majority of hydrazine was excreted during the first 24 hours and in acetylated forms. Urinary levels of hydrazine were very similar within each dose group.

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11. in Male Fischer 344 Rats Following Inhalation or Intravenous Exposure.

PREFACE

This research was conducted in the Toxicology Branch, Toxic Hazards Division, Air Force Aerospace Medical Research Laboratory from November 1982 through March 1984. It was performed in support of Project 6302, "Occupational and Environmental Toxic Hazards in Air Force Operations;" Task 630208, "Toxicology of Aerospace Fuels;" Work Unit 63020804, "Chronic Toxicology of Hydrazine Strategic Missile Fuels."

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INTRODUCTION

Hydrazine, a strong reducing agent, is used extensively in industrial processes and in military propulsion systems. The toxic properties of hydrazine have been recognized for some time. In 1978, the National Institute for Occupational Safety and Health estimated that 9,000 workers in the United States were potentially exposed to hydrazine each year (NIOSH, 1978). Consequently, many researchers have investigated the acute and chronic toxicity of hydrazine and shown that hydrazine is well absorbed by all routes of administration, but that exposure in the workplace generally occurred through inhalation or contact with skin and eyes. In 1981, Keller and coworkers reported on the percutaneous toxicokinetics of hydrazine and H-70 (azeotropic mixture of 70% hydrazine and 30% water) in the rabbit. Groups of albino rabbits were given hydrazine percutaneously and serial blood samples taken from the femoral vein. The authors concluded that acute systemic toxicity correlated more closely with peak blood levels than with total amount absorbed (Keller et al., 1981). Keller et al. (1984) later expanded this study to include the percutaneous absorption of hydrazine in the rabbit when exposures were time-limited and conducted with more dilute aqueous solutions. Although a significant amount of hydrazine was absorbed from these dilute solutions, a greater percentage of hydrazine was absorbed as the hydrazine concentration increased. This suggests that the potential hazard hydrazine presents to the occupational environment may be greater than originally anticipated.

Using the relationships developed by Keller and coworkers, it may be possible to estimate the hydrazine exposure potential of various occupational environments. The purpose of this study was to develop an analytical method with urine which could be used following an accidental exposure to hydrazine to aid in determining the extent of a worker's exposure. The development of a rapid biological method of this type would support judicious treatment.

METHODS

MATERIALS

Twenty-four Fischer 344 male rats approximately 5 months of age and weighing 348 $\pm$ 11 g were purchased from Charles River Breeding Laboratories. The rats were equally and randomly allocated to three inhalation exposure groups, and were then exposed in a nose-only chamber for one hour to hydrazine concentrations of 10, 60, or 500 ppm. Following exposure, the rats were placed in metabolism cages and urine collected at 24 and 48 hours, with water available *ad libitum*. All urine samples were collected in containers placed in ice baths to prevent hydrazine and hydrazine metabolite decomposition, and were subsequently frozen until metabolite analyses were performed. At 48 hours post-exposure, the rats were sacrificed by an anesthetic overdose of halothane. All exposures were conducted in a dynamic exposure chamber (0.45 m x 0.22 m x 0.55 m) constructed of 1cm thick plexiglass. Attached to the front of the chamber were twenty 6.7cm ID by 12.7cm long plexiglas tubes, each having chamber penetration so as to

allow for nose-only exposure. Each rat was restrained in the tube with a rubber stopper-secured plunger. The restraining tubes were rinsed with water following exposure, and the rinses analyzed by gas chromatography for hydrazine.

The chamber air inflow was 127 L/min as measured with a Fisher and Porter flowmeter (number 1/2-27-6-10/83, calibrated with a Collins Inc. chain compensated gasometer). The chamber exhaust port was located on the side opposite the intake port, and chamber pressure was maintained at ambient by balancing the exhaust vacuum. Exhaust was passed through a water scrubber system.

The chamber atmosphere was monitored and controlled using the method of Geiger and Vernot (1968). Samples were continuously drawn through a 1/4 inch polyflow tubing to a scrubber tower. The hydrazine was scrubbed with an absorber solution containing excess iodine, for complete reaction, and 40 g/L KI, 20 g/L Na_2HPO_4, and 6 g/L KH_2PO_4. The reacted absorber solution was pumped through the sample side of a Technicon Autoanalyzer colorimeter and compared to an unreacted absorber solution pumped through the reference side. The highest concentration exposures were run with 550 nm filters and the lowest concentration exposures were run with 420 nm filters. The solutions were pumped with a Technicon Autoanalyzer II proportioning pump and colorimeter output signal was recorded on a Soltec Model B181 strip chart recorder. The air sample was pulled into the scrubber tower with a Dia Pump, controlled with a valve and measured with a Fisher and Porter C-1420-TA-6-5 flowmeter.

Calibration was performed using standard bags. Contaminant was supplied through a Hoke tee in the input air line with syringes which varied in size according to the concentration desired. The syringes were driven with a Sage Model #355 syringe pump and liquid delivery was measured from syringe readings. The hydrazine was supplied by American Scientific Products and manufactured by Eastman Kodak Company, Rochester, New York.

Thirty-one additional Fischer 344 male rats approximately 4 months in age and weighing 295 $\pm$ 14 g were purchased from Charles River Breeding Laboratories. The rats were randomly allocated to three dose groups and each group given either 2, 6, or 12 mg/kg body weight of hydrazine intravenously. One day prior to exposure, each rat was anesthetized with a solution containing 70 mg/mL ketamine and 1.8 mg/mL xylazine given intraperitoneally at 1.0 mL/kg body weight and a 22 gauge, 8 inch long polyethylene cannula was placed in a femoral vein. The hydrazine doses were administered the day after surgery through the cannula in five boluses, fifteen minutes apart. To ensure that each animal received an equal volume of fluid, hydrazine was diluted with physiological saline of sufficient quantity to make a 0.6 mL total volume dose. Following exposure, the rats were placed in metabolism cages for 24 and 48 hour urine collection, with water available ad libitum. To prevent dehydration and to encourage urine flow, each animal was given 5.0 mL physiologic saline solution intraperitoneally twice daily for two days. All urine samples were collected in containers placed in ice baths to slow bacterial decomposition

of urinary components, and were subsequently frozen until metabolite analyses were performed. At the end of the urine collection period, the rats were sacrificed by anesthetic overdose.

ANALYTICAL PROCEDURES

Urinary levels of hydrazine and two metabolites, monoacetylhydrazine and diacetylhydrazine, were determined by gas chromatography using the chlorobenzaldehyde technique of George (personal communication) described below. C_{18} Sep-pak ™ tubes (Waters Associates, Inc., Milford, MA) were used to prepare individual urine samples for analysis by gas chromatography. The urine collected from study animals was allowed to thaw at room temperature. Equal volume aliquots of urine from rats at each dose level were eluted through Sep-pak columns into a 50 mL centrifuge tube. One mL of an aqueous 1% solution of acetic acid per 2.0 mL urine was used to lower the pH of the samples. A 2.5% solution of chlorobenzaldehyde in methanol was added to form derivatives of hydrazine and acetylated hydrazine. Twenty-five mg of chlorobenzaldehyde was added per milliliter of eluted sample. The samples were then incubated in a water bath at 45°C for 2.5 hours, with mixing every 30 minutes. Following incubation, the aliquots were cooled to room temperature and extracted with 5 mL of methylene chloride. The samples were centrifuged for 10 minutes at 3,000 G and the bottom (organic) layer removed and placed in a 50 mL centrifuge tube. The samples were extracted with methylene chloride four more times and the extracts combined and dried over anhydrous sodium sulfate. They were then concentrated in a Buchner Evaporator at 25°C and each dried sample dissolved in 1 mL of ethyl acetate for analysis by gas chromatography. To determine the urinary levels of diacetylhydrazine, 0.3 mL of concentrated hydrochloric acid was added to the aqueous layer of the methylene chloride-extract and the samples incubated in a 45°C water bath overnight. Following incubation, the same extraction procedures, starting with chlorobenzaldehyde derivatization, were followed.

To confirm the presence of, and quantitate, hydrazine and hydrazine metabolites in urine extracts, and to determine if detector response to these compounds was uniform, various concentrations were added to random control urine samples and used as standards. The standards were analyzed by gas chromatography and the detector response, reported in peak area, determined.

A Hewlett-Packard 5880A gas chromatograph equipped with a flame ionization detector was used to determine the urinary levels of hydrazine and hydrazine metabolite derivatives. A 6ft x 1/8 inch glass column packed with 3% SP-1000 on 100/120 Supelcoport was used and the oven temperature programmed from 125°C to 250°C at 8°/min, after an initial delay of one minute, and held at final temperature for 10 minutes. Detector and injection port temperatures were 300°C and 250°C, respectively. Helium was used as the carrier gas with a flow rate of 30 mL/minute.

RESULTS AND DISCUSSION

Hydrazine and two metabolites, monoacetylhydrazine and diacetyl-hydrazine, were identified and quantified in the urine of hydrazine-exposed

male rats. A representative gas chromatographic tracing of a urine sample from a male rat exposed to hydrazine, and one of control male rat urine spiked with 25 µg of hydrazine and 50 µg of monoacetylhydrazine per milliliter are shown in Figure 1 and Figure 2, respectively. All unlabeled peaks correspond to peaks identified in normal unexposed male rat urine. During the chlorobenzaldehyde derivatization, diacetylhydrazine was hydrolyzed to form the parent compound and, therefore, detected and quantified as hydrazine.

Table 1 and Table 2 show the amount of hydrazine recovered following intravenous hydrazine administration in µg/mL urine and percent dose, respectively. Table 3 displays the amount of hydrazine recovered in µg/mL urine following inhalation exposure to hydrazine for one hour. For all intravenous and inhalation exposure groups, the majority of the hydrazine was excreted during the first 24 hours when compared to the amount excreted during the second 24 hours (48 hr collection). Furthermore, a greater percentage of hydrazine was excreted in the acetylated hydrazine forms, monoacetyl and diacetyl, than as free hydrazine. While the amount of urine excreted from each animal varied tremendously, the levels of hydrazine detected in the urine were very similar within each dose group. For intravenous hydrazine administrations, a larger dosage resulted in a greater percentage of hydrazine recovered in both 24 and 48 hour urine collections. For example, the percent dose recovered during the 24 hour urine collection period was 14% for the 2 mg/kg B.W. group and 16% for the 6 mg/kg B.W. group, whereas, 33% of the total hydrazine dose was recovered in the 12 mg/kg B.W. group.

When comparing hydrazine recovery from intravenous and inhalation exposures, the total amount of hydrazine recovered was used since the concentration of recovered hydrazine metabolites was relatively small. The 500 ppm inhalation exposure group was the only inhalation exposure level that resulted in a total hydrazine recovery within the range of the hydrazine recovery from intravenous exposures. These data are shown in Table 4. The estimated equivalent intravenous dose for this inhalation exposure was 9.8 mg/kg. The other inhalation exposures resulted in total hydrazine recoveries that were not within range of the hydrazine recovery from intravenous exposures. Therefore, estimated equivalent intravenous doses could not be calculated with any confidence. However, it is important to note that when the 500 ppm exposure level is converted from concentration in ppm to an estimated dose received in mg/kg using the formula listed below, the calculated equivalent intravenous dose is 8.3 mg/kg. This value is comparable with the intravenous dose of 9.8 mg/kg determined from the data.

$$\text{Conc in PPM} \times \frac{\text{M.W.}}{\text{Vol of 1 mol gas at 25°C}} = \text{mg/m}^3$$

$$\frac{\text{mg}}{\text{kg B.W.}} = \frac{\text{mg}}{\text{m}^3} \times \text{respiratory minute vol. (mL/min)} \times \text{exp. duration (min)} \times \frac{\text{m}^3}{10^6\text{mL}}$$

$$\text{Body Weight (kg)}$$

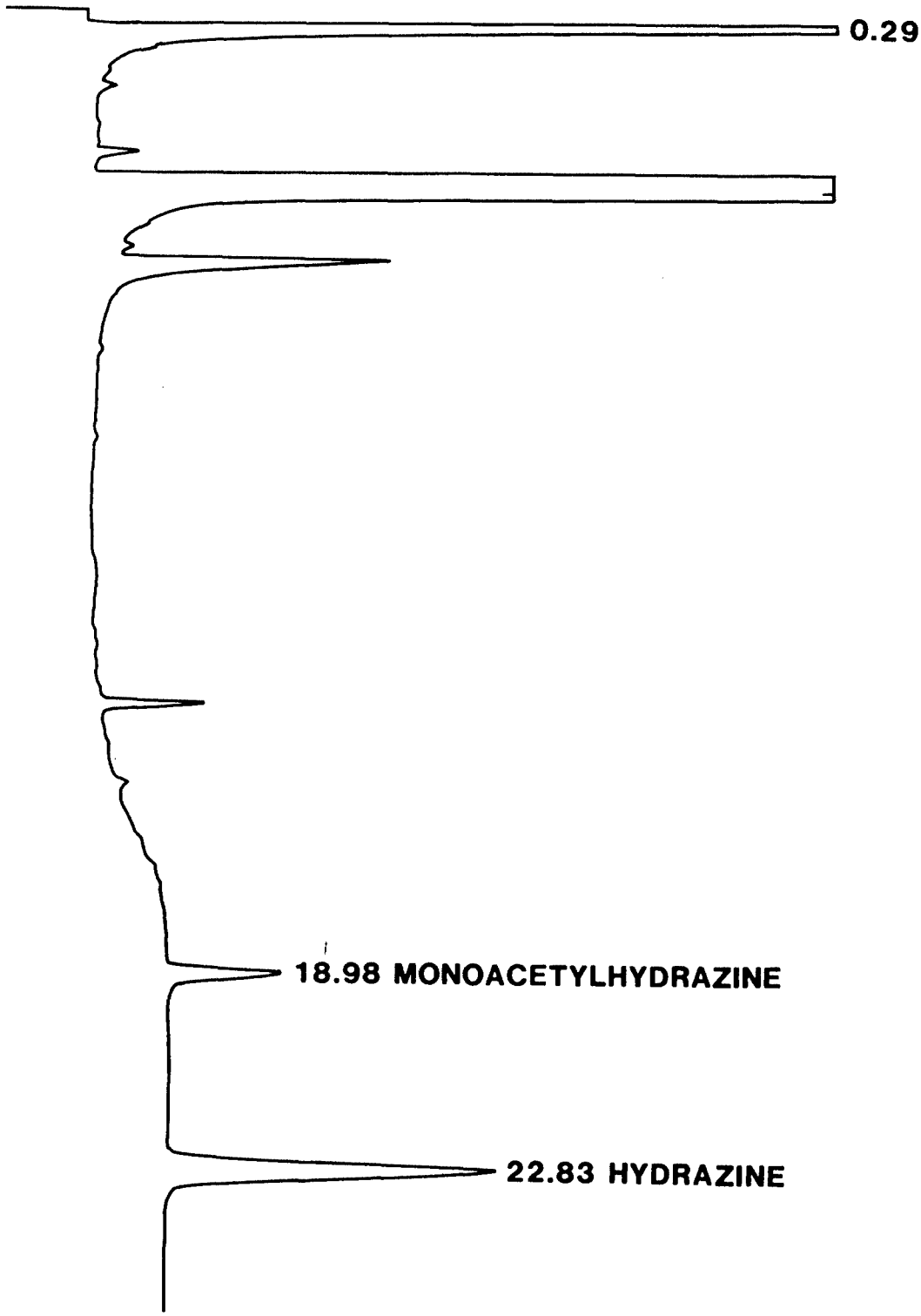

Figure 1. REPRESENTATIVE GAS CHROMATOGRAPHIC TRACING OF URINE FROM MALE RATS EXPOSED TO HYDRAZINE

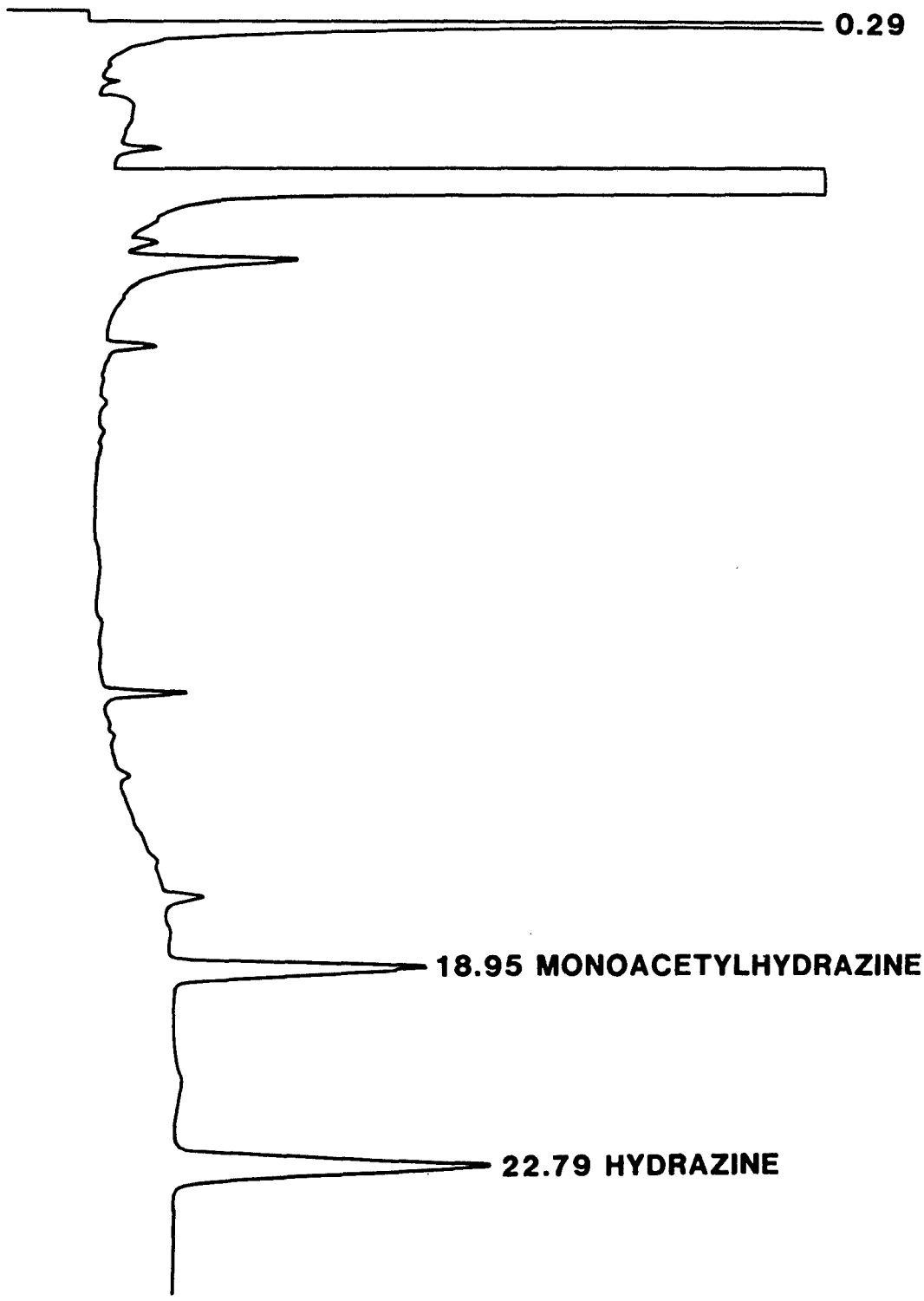

Figure 2. GAS CHROMATOGRAPHIC TRACING OF UNEXPOSED MALE RAT URINE SPIKED WITH 25 µg OF HYDRAZINE AND 50 µg OF MONOACETYLHYDRAZINE PER MILLILITER

TABLE 1. AMOUNT OF HYDRAZINE RECOVERED IN μG/ML URINE FOLLOWING INTRAVENOUS HYDRAZINE ADMINISTRATION

Dose and (N) μg	Collection Time (hrs)	Amount of Urine Excreted (mL)	Amount of Hydrazine Recovered [a] FHz	MHz	DHz
598 ± 15(9)	24	13.5 ± 5.1 (Range:7.0 - 24.0)	1.8 ± 0.8	2.4 ± 0.8	2.2 ± 0.7
1858 ± 64(9)	24	10.6 ± 6.5 (Range:5.4 - 23.6)	4.7 ± 1.7	7.5 ± 2.9	16.0 ± 6.4
3396 ± 57(12)	24	12.6 ± 4.2 (Range:7.4 - 21.8)	50.8 ± 32.2	16.6 ± 7.0	98.9 ± 44.6
598 ± 15 (9)	48	11.0 ± 5.1 (Range:5.0 - 20.2)	ND≤ 0.001	ND ≤0.001	ND ≤0.001
1858 ± 64 (9)	48	12.0 ± 5.4 (Range:4.6 - 20.8)	0.6 ± 0.34	3.1 ± 1.1	ND ≤0.001
3396 ± 57 (11)	48	8.1 ± 3.5 (Range:7.4 - 21.8)	5.0 ± 4.3	7.3 ± 4.2	18.5 ± 5.3

a = Values were determined by comparing G.C. peak areas of experimental animals to standard G.C. peak areas and expressed in μg Hz/mL urine as mean ± S.D. N = The number of animals used for obtaining means and standard deviations. Abbreviations used in this table are: FHz (Free Hydrazine), MHz (Monoacetylhydrazine), DHz (Diacetylhydrazine), and ND (Non-Detectable).

TABLE 2. PERCENT DOSE OF HYDRAZINE RECOVERED FROM RAT URINE FOLLOWING INTRAVENOUS HYDRAZINE ADMINISTRATION

Dose and (N) (μg)	Collection Time (hrs)	Amount of Urine Excreted (mL)	Percent Dose Recovered[a] FHz	MHz	DHz	Total Hz
598 ± 15(9)	24	13.5 ± 5.1 (Range: 7.0 - 24.0)	4.0 ± 1.9	5.2 ± 1.9	4.6 ± 1.5	13.8 ± 4.6
1858 ± 64(9)	24	10.6 ± 6.5 (Range: 5.4 - 23.6)	3.1 ± 2.1	4.0 ± 2.1	8.8 ± 2.4	15.9 ± 3.5
3396 ± 57(12)	24	12.6 ± 4.2 (Range: 7.4 - 21.8)	16.9 ± 7.7	6.0 ± 2.7	10.4 ± 6.5	33.3 ± 11.3
598 ± 15(9)	48	11.0 ± 5.1 (Range: 5.0 - 20.2)	ND ≤ 0.001	ND ≤ 0.001	ND ≤ 0.001	ND ≤ 0.001
1858 ± 64(9)	48	12.0 ± 5.4 (Range: 4.6 - 20.8)	0.4 ± 5.34	1.7 ± 0.51	ND ≤ 0.001	2.1 ± 0.71
3396 ± 57(11)	48	8.1 ± 3.5 (Range: 7.4 - 21.8)	1.2 ± 0.9	1.7 ± 0.9	1.3 ± 0.7	4.0 ± 0.9

a = Values were determined by comparing G.C. peak areas of experimental animals to to standard G.C. peak areas and expressed in μg Hz/mL urine as mean ± S.D. N = The number of animals used to obtain means standard deviations. Abbreviations used in this table are: Hz (Hydrazine), FHz (Free Hydrazine), MHz (Monoacetylhydrazine), DHz (Diacetylhydrazine), and ND (Non-Detectable).

TABLE 3. AMOUNT OF HYDRAZINE RECOVERED IN µG/ML URINE FOLLOWING INHALATION EXPOSURE FOR ONE HOUR TO HYDRAZINE

Exposure Concentration and (N) (mg/m^3)	Collection Time (hrs)	Amount Of Urine Excreted (mL)	AMOUNT OF HYDRAZINE RECOVERED (µg Hz/mL Urine) [a] FHz	MHz	DHz
7.36 (8)	24	11.3 ± 3.5 (Range: 8.0 - 18.8)	0.17 ± 0.05	0.13 ± 0.08	0.35 ± 0.12
44.2 (8)	24	12.5 ± 2.1 (Range: 9.0 - 15.4)	1.12 ± 0.47	1.41 ± 0.31	1.45 ± 0.37
368.0 (8)	24	18.2 ± 6.6 (Range:10.0 - 20.0)	24.56 ± 6.21	9.68 ± 1.53	27.78 ± 9.80
7.36 (8)	48	11.9 ± 3.8 (Range: 8.6 - 19.6)	ND ≤ 0.001	ND ≤ 0.001	0.005 ± 0.002
44.2 (7)	48	12.1 ± 3.4 (Range: 9.0 - 17.6)	ND ≤ 0.001	ND ≤ 0.001	ND ≤ 0.001
368.0 (8)	48	12.2 ± 3.1 (Range: 7.6 - 17.0)	3.78 ± 2.40	4.17 ± 1.47	6.97 ± 3.35

a = Values were determined by comparing G.C. peak areas of experimental animals to standard G.C. peak areas and expressed in µg Hz/mL urine as mean ± S.D. N = The number of animals used to obtain means and standard deviations. Abbreviations used in this table are: Hz (Hydrazine), FHz (Free Hydrazine), MHz (Monoacetylhydrazine), DHz (Diacetylhydrazine), and ND (Non-Detectable).

The feasibility of developing a method that would utilize urine metabolite identification and quantification to estimate the dose received from hydrazine inhalation exposure in rats was studied. Presently, the method is in a developmental stage and additional data must be collected before it can be proposed for use in estimating human exposure.

TABLE 4. HYDRAZINE RECOVERY IN Mg/Kg B.W. FROM RAT URINE FOLLOWING INTRAVENOUS HYDRAZINE ADMINISTRATION

		Hydrazine Recovered (mg/kg)[a]
DOSE and (N)	COLLECTION TIME (hrs)	TOTAL Hz
2 mg/kg (9)	24	0.277 ± 0.091
6 mg/kg (9)	24	0.951 ± 0.209
12 mg/kg (12)	24	4.020 ± 1.380
500 PPM (8)	24	3.170 ± 0.616

a = Values were determined by comparing G.C. peak areas of experimental animals to standard G.C. peak areas and expressed in μg Hz/mL urine as mean ± S.D.. N = The number of animals used to obtain means and standard derivations.

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